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MUCORMYCOSIS: AN EMERGING BLACK FUNGUS RISK

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ABSTRACT

Mucormycosis is a life threatening and rare fungal infection. It emerged as a significant warning due its foremost wild exposure on humans can affect various parts of the body which involves Sinuses, Skin, lungs & gastrointestinal tract. Symptoms are firstly Headache, Nasal and Sinus congestion follow Fever, Cough, Black Lesions & Swelling on face.

It is also known as BLACK FUNGUS. This abstract gives an overview on fungal infection and emphasize the requirements for spreading awarness and research to better perception on this daunting infection. Mucormycosis observed in patient those treated with corticosteroids in recent COVID-19 era and this infection often linked to underlying conditions like Diabetes Mellitus, DKA, endothelialitis, lymphopenia, Radiation therapy and also organ transplants. This includes early diagnosis and through tissue biopsy and monitoring computed tomography scan [CT].The key to successful treatment includes Antifungal drugs, control underlying conditions, hyperbaric oxygen, and surgical debridement this can improve the survival of patients.

Keywords: Mucormycosis, COVID-19, Black fungus, Diabetes mellitus, fungal infection.

INTRODUCTION

Mucormycosis, is termed as 'black fungus, it is rare and has heightened strength to attack the humans. It's been grabbing the attention due to recent increase in mortality, Of course it occurs through inhaled fungus spores and comes into contact with open Wounds. Furthermore this fungi belongs to the order Mucorales, eg:Rhizopus and mucor [4, 5]. It represents in various clinical forms based on site of infection:

1. Rhino-cerebral Mucormycosis: The genera Rhizopus, Mucor & Rhizomucor are the main culprits for this form of mucormycosis. This especially affects the Sinuses and could travel to the brain. Symptoms like facial pain, nasal congestion, and visual disturbance. Patients with weakened immune system and underlying diabetes are the spotlight [1].

2. Pulmonary Mucormycosis: This effects in the respiratory system i.e. Mostly in the Airways and lungs tissues and may open on to lung tissue Necrosis. Systems are cough, Chest pain, SOB and coughing of blood. Hematological malignancies, Neutropenia and uncontrolled diabetes patients have higher risk of pulmonary mucormycosis [3].

3. Cutaneous Mucormycosis: Site of action beings with a cut on the skin or mostly through open wounds, surgical incision and then fungi spreads into the underlying skin tissue. This form of infection is rare. Skin appears to be red, swollen, painful and also tissue death cause black Eschar. Patient with weakened immune system and uncontrolled diabetes are prone to infection [8, 9].

4. Gastrointestinal Mucormycosis: This mostly involves the stomach, ileum, colon and liver and affects in the severely malnourished patients and also in organ transplants [9].

5. Disseminated Mucormycosis: Spread through the bloodstream then other parts of the also involves brain, kidneys, heart. Patients with immunosuppressive therapies, organ transplant, are at high risk of developing disseminated Mucormycosis [8].

UNDERLYING CONDITIONS THAT ARE SPOTLIGHT FOR MUCORMYCOSIS:

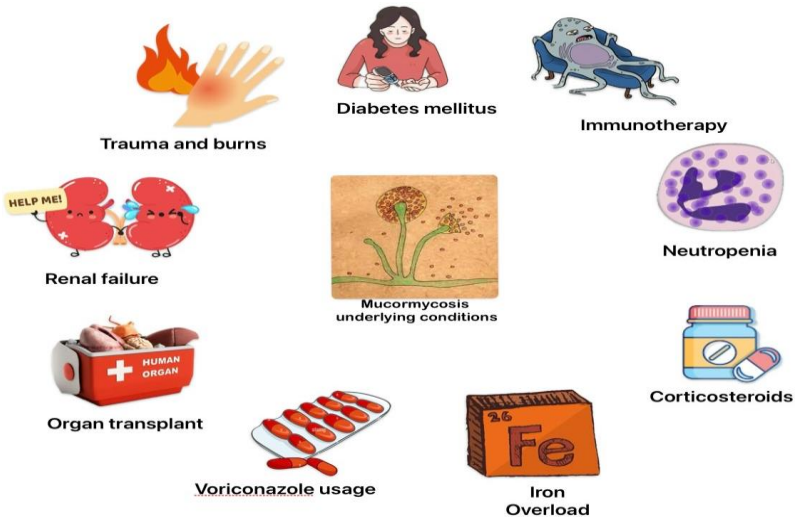

Fig 1: Underlying conditions of mucormycosis.

Diabetes mellitus: It is a disorder of endocrine system, which is insulin deficient or resistant to insulin/unable to process sugar. The supremacy of diabetes mellitus is rising which Causes Weakened Immune System Mostly spotlight for fungal infection in DM Patients with diabetes are more prone to infection than in a healthy individual. Fungi lives in high glucose level environment, which is the reason for fungi to flourish in uncontrolled diabetes and also black fungus is aggressive towards blood vessels which causes invasion of blood vessels which is also similar conditions in diabetes so these risk could make possible to spread the infection[11].

Diabetes Ketoacidosis: It is possible risk to the body where it produces excess blood acids or ketones occurs when there is as severe deficiency of insulin, leads to rise in blood sugar levels impairs severe deficiency of insulin, leads to rise in blood sugar levels impairs the WBC function making it more prone to infection also DKA weaken the immune system response to infection[10].

Hematological Malignancy: It is starting stage of forming cancer, where there is wild growth of abnormal cells and in blood forming tissues. Hematological malignancy such as Leukemia, Lymphomas and multiple myeloma are also threat for occurring infections, some studies say that patients with HM and mucor mostly have acute myeloid Leukemia. These needs rigorous treatment which includes chemo, this declines the body's natural defense leads to weak immune system which is spotlight for infection [2].

Corticosteroids: They are Anti-inflammatory medications, prolong use of corticosteroids leads to reduce migration, endolysosme fusion in Macrophages and damages Neutrophils and induce DM in patients. Studies say that more than 3 weeks use of corticosteroids i.e. high dose will be a spotlight for infection and also Corticosteroids usage in COVID-19 era patients are rigorously exposed to Mucormycosis [9].

Free Iron/Iron Overload: The accessibility of free iron is said to be underlying factor, In Humans iron is not as accessible to fungi as Iron is attached to proteins. Siderophores are the Iron-chelating molecules produced by fungi which helps to acquire iron. Likewise uncontrolled DM, Hyperglycemia and Acidic tissue environment enhance releasing more free iron which is more accessible for fungi to thrive which progress the infection also serum iron is increased in Dialysis patient during this procedure Deferoxamine an Iron-chelating drug is suggested for dialysis patient which helps to reduce excess iron but there is rare case which is a risk factor for Mucormycosis [10].

Other: Multiple studies describe that Underlying conditions for black fungus like Neutropenia, Burns, Trauma, Malnutrition in children, IV drugs use, Solid organ transplant, Immunosuppression are said to be spotlight for Mucormycosis [2].

DIAGNOSIS:

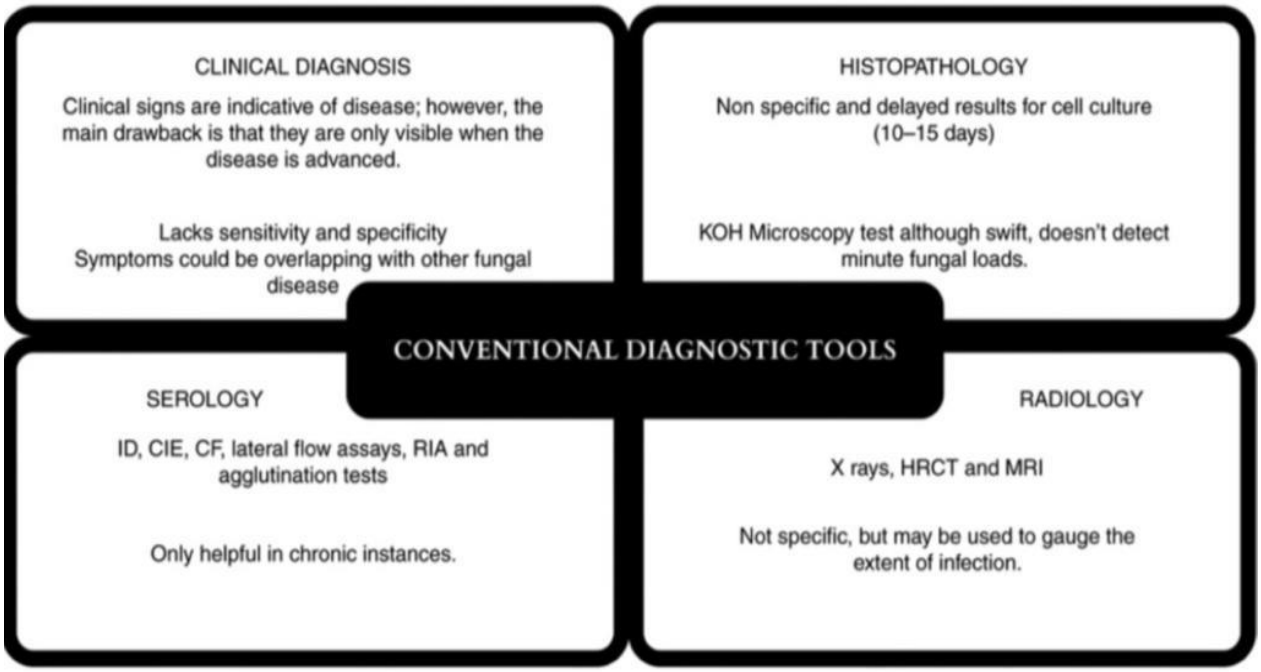

Fig 2: Conventional diagnosis tools [11]

Mortality rate linked with Mucormycosis is rising rapidly, because of no spontaneous diagnosis and delaying in controlling infection. Diagnosis tests depends upon the clinicals presentation and site of infection. Usually it involves Laboratory tests, clinical evaluation, and imaging studies [11]. Mucorale have been described as having broad, ribbon, like twisted aseptate hyphae with right angle branching.

Radiology: Radiology is elite diagnostic tool, it involves techniques like MRI and CT. MRI is metric standard than the CT is frequently used and sensitive radiology tool. Infection can be seen within 1st week of illness in 94% of cases. Likewise ENT [ear nose throat] Endoscopy is necessary and should repeatedly checked for response to treatment. However, CT scan doesn't accurately shows the fungal etiology [11]. Mucor also associated with numerous nodules and pleural effusion on radiology, presence of RHS [Reverse Halo symbol] is perfect sign of mucor. PET [position emission tomography]/CT with Fluorodeoxyglucose is also other raising imaging policy [12].

Culture/Microbiological: In this they collect the samples from site of infection, and observe in laboratory to identify the specific fungi causing infection. Various techniques such as mucor fungi bloom rapidly on most fungal culture media eg: potato dextrose and sabouraud agar incubated at 25-30°C [3-7] days. Culture diagnosis gives information on the specific genus and species level, moreover they are observed under microscopic specifically utilizing calcofluor and blankophor. Fungal elements are identified upon hematoxylin and eosin parts. Gomori's methenamine silver staining is for identifying fungal hyphae and also detailed analysis [7]. Flex of bronchoalveolar lavage is low for diagnosis of pathogen in patients with hematology and early bronchoscopy before Antifungal drugs use may provide good chance for diagnosis [6].

Biopsy: It is way to confirm the diagnosis, and is often necessary. A sample is collected from site of infection then observed. On other hand Tissue biopsy differentiates existences of fungi as a pathogen in a tissue and presence of a culture contaminant [12].

Molecular Diagnosis: This diagnosis used for identifying early stage of infection, helps to lead early evaluations and outcomes. It gives information on specific species cause for infection which is crucial for treatment. There are various ways of molecular methods such as, polymerase chain reaction, different primers or DNA barcodes, FTR1 molecular marker, whole genome sequence. PCR is a non-invasive technique by using different primers the identification and classification of Mucorales is made, it also has several benefits like less error rate, small DNA sample is required and rapid results.[6] The successfully tested FTR1 molecular maker identified species such as genera Rhizopus, Rhizomucor and Syncephalastrum. Whole genome sequence is a connecting bridge between various cases with various strains of Mucorales from various outbreaks helps to understand the epidemiology of outbreaks. Moreover, molecular methods are more definitive than the other diagnostic procedures as they consumes lot of time. This sort of infection is in need of hasten diagnostic procedure and that is molecular methods[8].

Serology: Serology techniques are vast in identifying the antibodies the antibodies of fungi as a diagnostic tool. Immunoassays, Immunodiffusion, complement fixation [CF], later flow test, radio- immunosorbent assays are some tools are used for identifying. Advanced serology methods recently showed that enzyme-linked immunospots [ELISpot] assay has been used to identify Mucorales specific T cells. Small disadvantages of this tool is time intensive [10].

TREATMENT

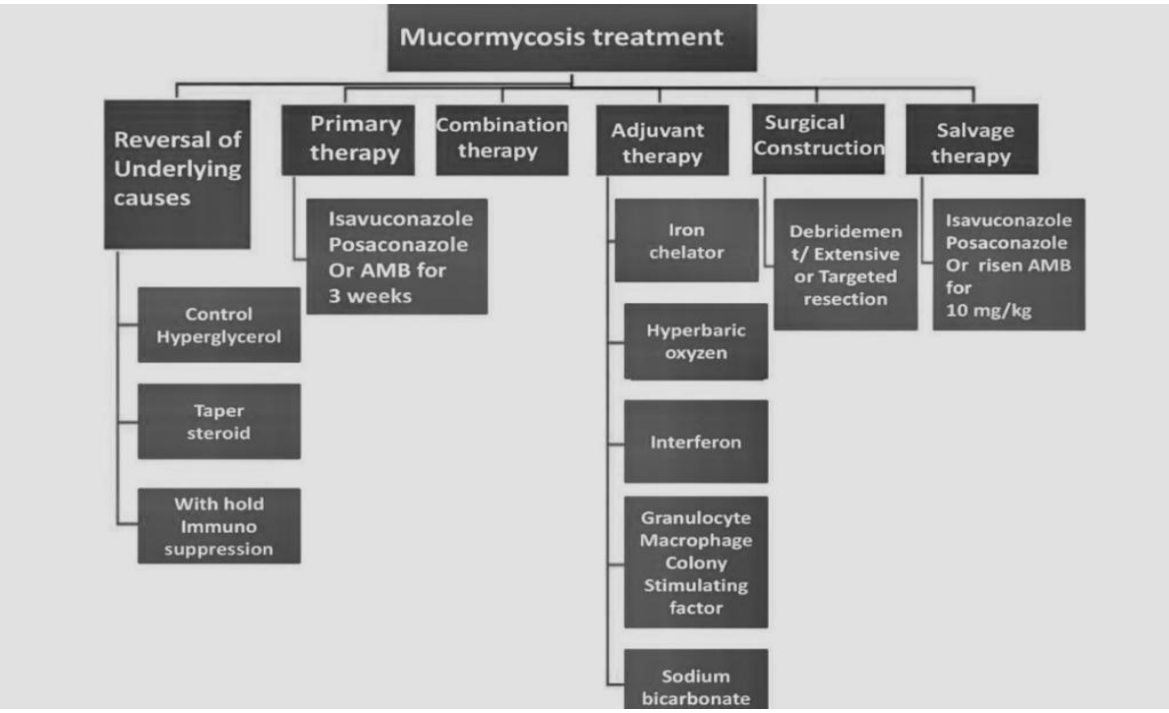

Fig 3: Source from Folia Microbiologica

The therapy involved in Mucormycosis is combination of Antifungals and surgical innervations. The mechanism of action of antifungals medications is drug binds to Ergosterol in fungal cell membrane which causes cell necrosis. The aim of therapy involves pausing the progressive infection, saving affected tissue, and controlling the underlying conditions. There are few ways of increasing the survival rate of patients suffering from rare infection includes:

Antifungal Medications: Antifungals medications plays the crucial role in rising the survival rate of patients, fights rigorously against the stubborn infection [1]. Antifungals has specific agent in-vitro to Mucorales. Amphotericin B acts as a first line therapy, and successfully used against mucormycosis and shown less mortality. As per European guidelines utilization of lipid formulations of Amphotericin B as 1st line therapy has more chance of survival rate. Voriconazole has shown no useful action against Mucorales [7]. Moreover combination of antifungal drugs shown high survival rate, in case pulmonary mucormycosis therapy includes combination of drugs i.e. Ciprofloxacin/Trovafloxacin in combination with Fluconazole fights against the infection. Acute myelogenous leukemia with pulmonary mucormycosis treated with Amphotericin B and 5 Flucytosine. Combination of Amphotericin B and Caspfungi gives higher outcomes in Rhinocerebral mucormycosis [1]. Amphotericin B is active medication against infection except for some *Cunninghamella and Apophysomyces* isolates. Posaconazole and Isavuconazole are active against the infection same as Itraconazole and Terbinafine shows same action against the certain strains.[5] some Mucorales like *R.oryzae,* have less susceptibility to natural host defence, as compared to other fungi like Aspergillus or candida making them more risk to treat also leads to increased mortality [1, 6].

Surgery: Surgery is necessary in few cases and it has opportunity for successful survival. Surgery is proceed when it is needed. And it is not only pullout the infected tissue but also the surrounding healthy looking tissue. Thus process is needed and most useful in case of Rhinocerebral mucormycosis, and in pullout single lesions, as it is impossible in cases of disseminated mucormycosis, as it reaches out organs like the brain, lungs, and important vessels.[11] As studies say that survival chances are increased through antifungal agents in addition with surgery [3].

Hyperbaric oxygen: ASIT is a supportive therapy, and specifically in some cases like site of infection like localized tissue with low blood supply in cases like sinuses and extremities. The decision of before proceeding with hyperbaric oxygen should consult expert HealthCare system as it is not confirmed as standard therapy [1]. this therapy proceeds through make attempt a more oxygen rich environment and administration of cytokines at same time with environment therapy, this results in specifically higher oxygen levels in the blood and tissue promoting healing tissue and body natural defense. While mucorale scan thrive in low oxygen levels whereas hyperbaric oxygen increase the oxygen levels which causes less possibility to fungi to thrive in host cells. And increasing oxygen levels can also heals the weakened immune system and boost the immune system action against the infection [1].

Immunocompromise reversal: Reversing Immunosuppression is an crucial role in fighting against the infection, if the patient is under medication that suppress the immune system, like corticosteroids , cutting them off is really good idea for reducing infection, this helps boost the immune system against the infection. And also providing nutritional support is ideal for maintain strong immune system. Healthcare providers consider using granulocytes macrophages colony stimulating factor and or interferon-Y may enhance the immune system fight against the mucormycosis[12].

Other: VT-1161[investigational drugs] as ergosterol synthesis inhibitor has specific activity against fungal CYP51 has in-vitro action against *R.Oryzae*, *lichthemia and cunninghamella,* shows high survival of Neutropenia with mucormycosis [11].

CONCLUSION

MUCORMYCOSIS is rare and threatening infection which is growing rigorously. Society is unaware of their diabetic, chronic kidney disease, pulmonary disease until they develop mucormycosis and so they are underlying conditions for infection. Due to delay in seeking help from healthcare professionals cause difficulty in diagnosing and controlling the advanced stage of infection. Moreover rigorous usage of corticosteroids in COVID-19 era caused high spotlight for infection and underlying conditions and severity of infection and also classification of mucormycosis is based on site of infection and how advance the infection is, treatment is crucial role in fighting against the infection and it is now become alarming condition for each an everyone since COVID-19 pandemic has raised the incidence of mucormycosis. Amphotericin B plays an important role as it is considered as first line therapy to fight against the infection. Combination of Antifungals and surgery gives the better survival chances, and also there are no specific standards on therapy. Since the scenario of COVID-19 it lead to a better understanding and possibilities of discovering new management techniques and treatment protocols to bring down the mortality connected with treating mucormycosis.

REFERENCE

1. Ramalingam Suganya, Narasimhan Malathi, Vinithra Karthikeyan and Vyshnavi Devi Janagaraj. 2019. MUCORMYCOSIS: A Brief Review. J Pure Appl Microbiol, **13** (1): 161-165.
2. Sharma A, Goel A. 2022. Mucormycosis: risk factors, diagnosis, treatments, and challenges during COVID-19 Pandemic. Folia Microbiol (Praha), 67(3):363-387.
3. Robert G Hendrickson MD, Jonathan Olshaker md, Olly Duckett md. 1999. Rhinocerebral mucormycosis; A case of rare, but deadly disease. The Journal of Emergency Medicine, 17(4): 641-645.
4. George Petrikkos, Anna Skiada, Olivier Lortholary, Emmanuel Roilides, Thomas J Walsh, Dimitrios P Kontoyiannis. 2012. Epidemiology and clinical manifestation of mucormycosis. Clinical Infectious Diseases, 54(S1): S23-S24.

5. Landge S, Menon S, Chande C, Kulkarni M, Bhilkar K, Bade J, Joshi A. 2023. A prospective study on emergence of mucormycosis in recently recovered COVID-19 patients. International Journal of Research in Medical Sciences, 11(7): 2498–2502.

6. Mehrabi Z, Salimi M, Niknam K, Mohammadi F, Mamaghani HJ, Sasani MR, Ashraf MJ, Salimi A, Zahedroozegar MH, Erfani Z. Sinoorbital Mucormycosis Associated with Corticosteroid Therapy in COVID-19 Infection. Case Rep Ophthalmol Med. 2021, https://doi.org/10.1155/2021/9745701

7. Feba V. Raju, Saramma Mathew Fenn, Karthik Rajaram Mohan, Ravi Kumar. 2022. Review on mucormycosis-A gloom epoch. Journal of academy of dental education, 8(2): 37-41.

8. Shikha Mudgal , Shalinee Rao, Manju O Pai. 2022. Mucormycosis: A comparative update between conventional and molecular diagnosis strategies. Curr Med Mycol, 8(1):44-53.

9. Fang W, Wu J, Cheng M *et al.* 2023. Diagnosis of invasive fungal infections: Challenges and recent developments. J Biomed Sci, 30(1): 42.

10. Prabhu RM, Patel R. 2004. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect, 10(l):31-47.

11. Prakash, Hariprasath and Arunaloke Chakrabarti. "Global Epidemiology of Mucormycosis." *Journal of Fungi*, 2019, 5(1): 26.

12. Rohit V Pawal, Arjun B Girhe and Suhas R Kolekar. Mucormycosis and Treatment A Review. Acta Scientific Microbiology 5.1 (2022): 09-16.